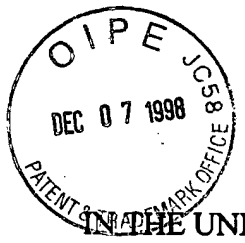

PATENT
Docket No. 223002006313
Client Ref. 0063.021

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

MICHAEL HOUGHTON et al.

Serial No.: 08/441,355

Filing Date: May 15, 1995

For: HCV IMMUNOGENS AND IMMUNOGENIC COMPOSITIONS

Examiner: M. Zeman

Group Art Unit: 1815

DECLARATION OF AMY WEINER, Ph.D.

I, AMY WEINER, HEREBY DECLARE AS FOLLOWS:

1. I am an Associate Director of Hepatitis Research at Chiron Corporation in Emeryville, California, the assignee of the subject application. A copy of my curriculum vitae, describing my background and qualifications, is attached to this Declaration as Exhibit A. I am not a named inventor on the subject application.

2. I hold a Ph.D. from the Molecular, Cellular and Developmental Biology program from Indiana University. I have worked in hepatitis research for 14 years.

3. As a result of the above experience, I have gained substantial expertise in the field of hepatitis research.

4. I have read the relevant sections of the above-referenced application as filed on May 15, 1995, pending claims 88 to 120 and the Office Action dated August 12, 1997.

5. It is well known to those of skill in the art that antigenicity as determined by the binding of antibodies to antigens reflects the immunogenicity of a polypeptide region. Methods for raising antibodies against an immunogenic composition comprising an immunogenic HCV polypeptide in substantially isolated form and measuring the binding of antibodies to the immunogenic composition were well known to those of skill in the art in 1987, and, are taught in the specification.

6. For example, the specification on page 59, line 23 through page 61, line 2, describes standard techniques known to those of skill in the art for raising antibodies against an immunogenic HCV composition and for measuring the binding of antibodies to the immunogenic composition. Generally these techniques described in the specification involve: 1) injecting a selected mammal (e.g., mouse, rabbit, goat, etc.) with an HCV polypeptide in substantially isolated form (candidate), 2) collecting the serum from the immunized animal, and 3) screening the serum for antibodies which bind to the candidate immunogenic HCV polypeptide using routine techniques known in the field, including for example, a radioimmunoassay, as described in section IV.D. "Radioimmunoassay for Detecting HCV Antibodies in Serum" on page 178, line 1 through page 179, line 24, or an ELISA, as described in the specification on page 25, lines 5-9.

7. It is my opinion as an expert in the field of hepatitis research, that the disclosure of the above-referenced application provides sufficient information to a

scientist of skill in the field applying routine procedures known in the field and materials available to that field to identify immunogenic HCV sequences.

8. For example, prospective polypeptide sequences need only be prepared and injected into a mammal with the appropriate carriers and/or adjuvants, as described in Section II.C. Preparation of Antigenic Polypeptides and Conjugation with Carrier - page 47, line 24 through page 53, line 36; and Section II.G. Preparation of Antibodies Against HCV Epitopes - page 59, line 23 through page 61, line 2, and then the serum collected and screened for antibodies which bind to the prospective polypeptide sequence using routine methods. Examples of routine screening methods include radioimmunoassay and ELISA, which are described in the specification on page 178, line 1 through page 179, line 24 and page 25, lines 5-9, respectfully.

9. Although, it is not necessary, to map a HCV epitope in order to practice the claimed invention such techniques are known to those of skill in the art and are taught in the specification. For example, the specification teaches methods for screening for immunological activity using routine techniques known to those of skill in the art, including for example, radioimmunoassay and ELISA. By starting with, for example, 20-mer polypeptides, it would be routine to test each polypeptide for the presence of epitopes showing a desired reactivity using, for example, a radioimmunoassay or an ELISA, and then testing progressively smaller and overlapping fragments from an identified 20-mer to map the epitope of interest (page 50, lines 2-20). Screening such peptides for immunological activity employs routine procedures known to those of skill in the art.

10. The specification teaches how to identify polypeptides which bind anti-HCV antibodies and not to antibodies directed against other viruses. As described in

the specification, on page 185, line 20 through page 186, line 5, the polypeptides of interest are first tested for immunoreactivity against sera from individuals which have been infected with non-HCV viruses (e.g. flaviviruses, HAV, HBV, etc...) using standard techniques, including for example solid phase RIA. By comparison, then, those polypeptides which bind specifically to antibodies in sera from those infected with HCV can be determined.

11. Furthermore, as described in the specification , it is known to those of skill in the art to carry out computer analysis of protein sequences to identify potential epitopes, and then prepare oligopeptides comprising the identified regions for screening. See for e.g. Hopp et al., *PNAS* (1981) 78:3824-3828. Such a computer analysis of the HCV amino acid sequence is shown in Figure 67, where the hydrophilic/hydrophobic character is displayed above the antigenic index (page 50, lines 20-32).

12. The specification teaches how to identify polypeptides which bind anti-HCV antibodies and not to antibodies directed against other viruses. For example, as described in the specification, on page 185, line 20 through page 186, line 5, the polypeptides of interest are first tested for immunoreactivity against sera from individuals which have been infected with non-HCV viruses (e.g. flaviviruses, HAV, HBV, etc...) using standard techniques, including for example solid phase RIA. By comparison, then, those polypeptides which bind specifically to antibodies in sera from those infected with HCV can be determined.

13. Each of the references cited by the Office are directed to NANB hepatitis. The disease NANB hepatitis is known to be caused by a variety of agents, including but not limited to, HCV, HEV, HDV and possibly HGV. Thus, an individual infected with an agent causing NANB hepatitis is not necessarily infected with HCV.

14. The position stated in the August 12, 1997 Office Action, on page 6, that Bradley et al. disclose viral preparations comprising at least 8 amino acids of HCV sequence and provoke an immune response is incorrect for the reasons stated in paragraphs 15 to 18.

15. Bradley et al. fail to demonstrate any evidence of an immune response to a composition containing an immunogenic HCV polypeptide which is in substantially isolated form wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof.

16. One of the two alleged agents Bradley et al. claim to have isolated has a buoyant density of 1.24 g/cc of CsCl. It is well known, however, to those of skill in the art, that HCV has a buoyant density of ~1.09 g/cc of CsCl. See for example, Hijikata et al., (1993) J. of Virology, 67:1953-1958 (copy attached).

17. In my opinion as an expert in the field of hepatitis research it would not have been possible for one of skill in the art, without knowing the sequence of

HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins to take the description in Bradley et al. and combine it with his/her own knowledge of the art, and thereby be put in possession of an immunogenic hepatitis C virus (HCV) polypeptide in substantially isolated form wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof.

18. It is well known to those of skill in the art that the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins were not available to those of skill in the art until after 1989.

19. Like Bradley et al., He et al. fail to demonstrate any evidence of an immune response to a composition containing an immunogenic HCV polypeptide which is in substantially isolated form and which comprises an immunogenic polypeptide wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof.

20. He et al. fail to describe the isolation of any polypeptide from virus lipid envelope or any other cellular components with which the viral polypeptide is naturally associated in the viral particle. Only crude serum filtrate maintaining infectivity

is produced; i.e., no isolated peptides are disclosed. Such a crude inoculum could have contained any number of viruses, including multiple forms of NANB hepatitis.

21. One of skill in the art at the time would not have been able to take the information disclosed in He et al. i.e., that strain H has an estimated size between 30 and 60 nm in diameter, and combine it with his/her own knowledge of the art at the time, and thereby be put in possession of the claimed invention. In order to practice the claimed invention, which is directed not only to HCV but to specific domains of HCV (i.e. core, env, NS-1, NS-2), one would need to know the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins. The sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins were not known to those of skill in the art until after 1989.

22. It is well known to those of skill in the art that there are a number of viruses that have the same characteristics as those disclosed in He et al., including, for example those described by He et al. on page 639-640 (the alphaviruses, the flaviviruses, the hepadnaviruses, and the hepatitis D virus).

23. Prince et al. fail to demonstrate any evidence of an immune response to a composition containing an immunogenic HCV polypeptide which is in substantially isolated form wherein the immunogenic polypeptide comprises a region selected from the group consisting of an envelope domain, a core domain, a NS1 domain

and a NS2 domain of an HCV genome and immunogenic fragments and combinations thereof.

24. Prince et al. fail to disclose any purification process of any polypeptide, let alone an immunogenic HCV polypeptide in substantially isolated form wherein the immunogenic polypeptide comprises a region selected from the group consisting ofthe core, envelope, NS1 or NS2 domain of HCV in substantially isolated form or fragments or combinations thereof.

25. In my opinion as an expert in the field of hepatitis research, it would not have been possible for one of skill in the art, without knowing the sequence of HCV or portions thereof, the genomic structure of HCV, the identity of HCV, or antibodies that identified HCV proteins, to take the description in Prince et al. and combine it with his/her own knowledge of the art, and thereby be put in possession of the claimed invention.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the

validity of the application or any patent issuing thereon.

Date 11/17/98

Amy Weiner, Ph.D.